DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51, Room 2269, Silver Spring, MD 20993 Email: OPFBLAInspection483Responses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	10/18/2021 - 10/26/2021
	FEI NUMBER 3007647000

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Wim Blendeman, General Manager

FIRM NAME	STREET ADDRESS
Catalent Belgium S.A.	Font Saint Landry 10
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Brussels, BRU, B-1120	Drug Product Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1:

Failure to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed. Specifically,

a. Standard Operating Procedure STB-QA-0010, Deviation Management, v21 classifies deviations as minor, major or critical based on the calculation of a risk priority number, with a HEPA filter failure within a Grade A environment often classified as minor. Specifically, Deviation 327567 (Date of occurrence 04 March 2021) was for a HEPA filter failure on the (b) (4) fill line, with a breach at the HEPA filter frame. The location of the HEPA filter was (b) (4) with a settling plate in the near vicinity having recoveries of (b) (4) CFU/plate. Your product quality impact assessment included within the deviation investigation failed to provide a comprehensive and detailed impact assessment for all products produced and distributed to the United States for the time period the Grade A environment was compromised and to prevent a recurrence of the failure. Commercial products manufactured within the compromised Grade A environment and distributed to the United States include the following:

i. Batch (b) (4)
ii. Batch (b) (4) mg, (b) (4) mL
iii. Batch (b) (4) mg (b) (4) mL
iv. Batch (b) (4) mg (b) (4) mL (b) (4)

b. You failed to adequately investigate multiple HEPA filter failures that were observed for the (b) (4) fill line Grade A space, Grade A/B space, and Grade B surrounding area, with the following filters replaced based on velocity (average speed) measurement not meeting the acceptance criteria of (b) (4) m/s to (b) (4) m/s, filter integrity for DOP test and differential pressure:

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May 2017, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause DOP and Average Speed
May 2017, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed
May 2017, Filter GTA02-LAF-0265.01-FA-13, Grade A/B, Root Cause Average Speed
May 2017, Filter GTA02-LAF-0265.01-FA-14, Grade A/B, Root Cause Average Speed

January 2018, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed
January 2018, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed

August 2018, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed
August 2018, Filter GTA02-LAF-0265.02-FA-01, Grade B, Root Cause Average Speed

March 2019, Filter GTA02-LAF-0265.02-FA-02, Grade A, Root Cause Average Speed

August 2019, Filter GTA02-LAF-0265.02-FA-01, Grade A, Root Cause Average Speed
August 2019, Filter GTA02-LAF-0265.01, Grade B, Root Cause DOP
August 2019, Filter GTA02-LAF-0265.02, Grade B, Root Cause DOP
August 2019, Filter GTA02-LAF-0265.03, Grade B, Root Cause DOP

March 2020, Filter GTA-LAF-0265.02-FA-02, Grade A, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.02-FA-01, Grade B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-13, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-14, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-15, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-16, Grade A/B, Root Cause Delta P
March 2020, Filter GTA-LAF-0265.01-FA-17, Grade B, Root Cause Delta P

March 2021, Filter GTA-LAF-0265.01-FA-08, Grade A, Root Cause Average Speed

A single commercial product produced on the (b) (4) fill line for United States distribution is (b) (4) (b) (4)

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Other GMP manufacturing areas have a similar elevated level of HEPA filter failures, with the root cause of the HEPA filter failures unknown. There is no CAPA in support of correction action. Your firm failed to ensure your investigations identify appropriate root causes and you failed to implement sustainable corrective action and preventive action (CAPA).

c. You failed to adequately investigate numerous environmental monitoring excursions for the GMP drug product manufacturing areas. Specifically,

In the calculation of environmental monitoring recovery rates for rooms in Grade B space from September 2020 to August 2021 (available data), a long term trend was observed where the acceptance limit was consistently exceeded, recovery rates ≥(b)(4)%. The trend includes the following areas: Area 297 Corridor; Room(b)(4) Women's Exit; Room(b)(4) Women's Entry; Room(b)(4) Men's Entry; Room 0403C, Personnel Exit, Men and Women; and Room(b)(4)

Furthermore, a similar trend for recovery rates not meeting the acceptance criteria was observed from March 2020 to June 2021 (available date) for Grade C Manufacturing, Grade C (b)(4) Shared Grade C space, and Grade D space, with the acceptance criteria for recovery rates Grade C and Grade D, ≤(b)(4)% and ≤(b)(4)%, respectively.

Corrective actions not limited to a procedural update, change control and CAPAs starting in October 2020 have failed to bring the recovery rates within the acceptance limit.

Observation 2:

Failure to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess. Specifically,

Your firm did not adequately validate the process used to manufacture the(b)(4) drug product.(b)(4) drug product stains on the exterior of the (b)(4) and drug product solution found in the stopper cavity is associated with (b)(4) dripping during manufacture on the (b)(4) fill line. You have not demonstrated that the filling process for the drug product is under control to ensure the prevention of contamination of(b)(4) drug product by

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equipment that could reasonably be expected to have an adverse effect on product quality.

Observation 3:

Validations, designed to prevent microbial contamination of the drug product purporting to be sterile, have not been adequately established. Specifically,

a. Rapport Validation Plan Equipment 131909-N Annex 4, 09 March 2008 for the RAB (b) (4) integrity tester includes a performance qualification where testing was conducted with a (b) (4) mm (b) (4) micrometer) breach, with the purpose of the test to evaluate the functionality of the instrument. The performance qualification failed to determine the breach limit of detection based on validation for the (b) (4) used on the (b) (4) fill line.

Furthermore, the integrity testing frequency for the (b) (4) is conducted (b) (4) The frequency is inadequate as it does not access the status of each batch that may be impacted by a (b) (4) failure.

b. The minimum load for (b) (4) sterilization is not reflective of the worst-case equipment item as determined from the maximum load (lowest acquired lethality item), but is based on a theoretical worst-case equipment assembly. Change control 151393 has been open since 18 November 2020 for a sterilization optimization study that includes a minimum load assessment based on the maximum load worst-case load item, with the sterilization studies still pending completion.

c. There is a failure to establish an equipment (b) (4) clean hold validation pending sterilization.

d. According to procedure STB-QA-0061, Methodologie de validation des procedures de nettoyage, v11, Effective date 08 Jan 2021, cleaning validation for vessel (tanks) includes rinsate samples, with swab samples excluded. Though rinsate samples may provide a good indication of cleanliness, it should not be used as a substitute for not performing swabbing on equipment that may present and elevated challenge in removal of product residues.

Observation 4:

A written procedure designed to prevent contamination of products during aseptic processing is not adequate.

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Specifically,

Procedure STB-MFG-0026, Generale Zone A/B, v10, Effective date 21 September 2021 contains instructions to sanitize, spray(b) (4) onto the RAB(b) (4) in Grade A space. On 20 October 2020, we observed your employee repeatedly spraying sterile(b) (4) within the (b) (4) RAB (Grade A space) during manufacture of (b) (4) to sanitize the RAB(b) (4) The practice occurred in close proximity to exposed stoppers within the stopper bowl and environmental monitoring that included a settling plate. A product quality impact assessment has not been performed to address the risk associated with the use of(b) (4) during manufacturing operations.

Observation 5:

Equipment and facilities used in the manufacture of drug product are not adequately maintained or appropriately designed to facilitate operations for their intended use. Specifically,

a. The (b) (4) filling machine RAB that extends to ceiling level and is (b) (4) system was observed with the (b) (4) barrier system damaged at a number of RAB (b) (4) points. The root cause of the damage is missing (b) (4)

Furthermore, two black lines were observed on a mechanical piston system for the (b) (4) near open(b) (4) You indicated the cause of the black material is unknown.

b (b) (4) sinks in Room(b) (4) Grade C space include a (b) (4) used in production equipment manual cleaning operations, with the sink drain line not containing a(b) (4) in mitigation of water backup.

c. Analytical balance BAL93 used in(b) (4) weight checks for the (b) (4) fill line was observed with the side shield glass broken, with the broken glass secured by tape.

d. Deteriorated surface finish sealant was observed within the following GMP suites: (b) (4) and Local Storage(b) (4) at the ceiling(b) (4)

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Observation 6:

Your laboratory analytical method for endotoxin has not been adequately validated. Specifically,

Procedure STB-QC-0048, Reception des escantillions au QC, v20, Effective date 06 August 2021 provides up to (b) (4) for the drug product in-process control endotoxin test. There is no validation to support the sample storage time of (b) (4)

Observation 7:

Standard operating procedures are not followed or are deficient. Specifically.

a. Standard operating procedures for visual inspection of the media fill (b) (4) SB-QC-0079 "Mirage des milieux de culture et (b) (4) MFT" v6.0, Effective date 30 Jan 2019 does not include instructions for mixing of samples prior to visual inspection.

b. Sample Logbook Suivi du Transfer des Echantilone, STB-QC-057-21, v2 was observed incomplete, with the date and hour for all entries, removal of material not completed. Procedure SOP-STB-QC-0057, Prelevement des Echantillions au Department Manufacturing, v7, Effective date 30 December 2020, Section 5.3.4 Transfert des echantillions, indicates to document transfers by logbook. The procedure was not followed.

Furthermore, Logbook Archivage Cycle Lancer, STB-MFG-0046-F3, v6, Effective date 23 March 2020 and Logbook D'Utilisation des (b) (4) au Department MFG, STB-MFG-0119-F1, v1, Effective date 25 September 2019 were not completed for Visa Paraphe Supervisor as required.

JA 10/26/2021

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